

REMARKS

Claims 1 through 20, where claims 1, 2, 5-7, 10 and 16 are as amended above, are pending following the entry of this Amendment. Claims 1, 5, 17 and 19 are independent claims.

Initially, Applicant wishes to thank the Examiner for the courteous personal interview between the undersigned attorney and Examiner Spivack on March 23, 2005, during which an Informal Draft Amendment was presented and discussed. The present Amendment has been revised compared to the Informal Draft Amendment in view of the interview. The substance of the interview is summarized below.

During the interview, the undersigned attorney explained the support in the application as filed for the amendments to the specification and claims as set forth in the Informal Draft Amendment. Such support is as follows. The last paragraph at page 3 and the designations of the structural formulas at page 4 for mesna and dimesna, respectively, have been re-designated in the application as Formulas A and B, rather than Formulas I and II, to avoid potential confusion with the later recitation of a different Formula I in the Summary and in the claims. Several paragraphs of the written description have been amended to correct typographical errors that will be apparent immediately upon reviewing the amendments, or to indicate that the invention relates not only to treatment of a patient or subject after radiation exposure but also to a prophylactic treatment of a patient or subject about to be exposed to ionizing radiation or about to undergo radiation therapy, consistent with and as supported by page 1, first paragraph, page 10, second full paragraph, and original claim 5, among other locations in the application as filed.

Compared to the Informal Draft Amendment, the present Amendment also revises the paragraphs at page 9, lines 4-10 and 11-16, and page 13, lines 3-11, to delete any reference to "thiethonate." The undersigned attorney learned after the interview that Applicant's assignee began an effort to establish "thiethonate" as a coined term for disodium 2,2'-dithiobis ethane sulfonate, also known as dimesna, but that Applicant's assignee has determined not to pursue this effort. Accordingly, rather than correct the spelling of "thiethonate" as proposed in the Informal Draft Amendment, to avoid potential confusion the present Amendment is canceling the term, as it is not needed.

Also as compared to the Informal Draft Amendment, the present Amendment revises the paragraphs at page 9, lines 17-19, and page 13, lines 3-11, and claims 1, 2 and 5-7 to refer to a human "subject" rather than a "patient." Claims 5, 7 and 10 also have been amended to recite exposure to radiation instead of a radiation therapy session. These amendments are supported by

the application as filed at page 10, lines 12-16, and were made to make it clear that the invention includes the situation where the human subject is or could be unintentionally exposed to ionizing radiation.

Claims 1 and 5 have been amended to correctly indicate, consistently, subscripts in the formulas. Claim 2 was amended to include a specific recitation of the compound of formula I as 2,2'-dithiobis ethane sulfonic acid, or a disodium salt thereof, as supported at least at page 9, line 6, of the application as filed. Claim 20 has been added to recite another preferred dosage range as supported at page 12, lines 7-8, of the application as filed, rather than including this dosage range in claim 2 as in the Informal Draft Amendment.

Additionally as compared to the Informal Draft Amendment, in the present Amendment claim 1 has been amended as discussed during the interview to make it even more clear that claim 1 relates to treating a subject after the subject has been exposed to ionizing radiation, even though this timing seemed clear prior to the amendment. Moreover, claim 5 has been amended to recite the intravenous or oral administration of the compound of formula I, in an amount to prophylactically protect the patient from adverse effects of ionizing radiation. Intravenous and oral administration is supported at least at page 12, lines 17-19, of the application as filed. Administration in an amount to prophylactically protect the subject against adverse effects of the ionizing radiation is supported at least in the paragraph bridging pages 12 and 13.

Claim 6 has been amended to more accurately state the dosage explanation based on body surface area of the subject, as one skilled in the art would readily understand that dosage in units of weight per m^2 means weight per body surface area of the subject receiving the dosage.

Further as compared to the Informal Draft Amendment, the present Amendment adds new claims 17-19, in addition to claim 20, discussed above. New independent claim 17 is supported at least by page 1, first paragraph, of the application as filed. Claim 17 excludes mesna as a compound of formula I.

New claim 18 depends from claim 17 and specifically recites that the compound of formula I is 2,2'-dithiobis ethane sulfonic acid, or a disodium salt thereof. This is supported at least by formula I at pages 8-9, as well as page 9, line 6, and page 13, lines 3-11, of the application as filed.

New independent claim 19 is supported at least by page 1, first paragraph of the application as filed and further by the disclosure at page 9, lines 4-6, of the application as filed.

The recitation relating to “serious adverse effects” in claim 19 is supported at least at page 3, lines 11-14, and page 4, line 14, to page 5, line 9.

No new matter has been added by any of the amendments to the specification or claims, and entry of the amendments is respectfully requested.

During the interview the undersigned attorney addressed all of the points that were raised in the Office Action. With reference to page 2 of the Detailed Action, claim 16 was corrected by adding a period and claim 2 was amended as indicated. It appears that the referenced amendment to claim 2 mentioned in the Remarks portion of the last Office Action response of July 12, 2004, was inadvertently not actually made in the amendment portion of that response. Thus, amended claim 2 now identifies dimesna and new claim 20 recites another preferred dosage range.

As part of the interview, the undersigned attorney and the Examiner then discussed the *Lancet* article, but during the interview, the Examiner initially was referring to a different article than the *Plowman et al.* letter, *Lancet*, January 17, 1987, page 167, (“Plowman”) as cited by the Examiner in the Office Action of April 7, 2003. Rather, initially during the interview, the Examiner was referring to a letter by Shaw *et al.*, *Lancet*, February 28, 1987, page 518, (“Shaw”) referring to the Plowman letter a month before. Shaw includes in its first sentence a statement that Plowman described studies in mice “in which mesna was shown to have radioprotective properties.” Although the Examiner referred to this language, the undersigned attorney pointed out that it only discloses such radioprotective properties with reference to the earlier Plowman letter, which, in turn, disclosed using a high dosage of mesna *i.p.* at least 12 hours before subjecting mice to total body irradiation (TBI). The Examiner then agreed that Shaw does not disclose any more than the Plowman letter.

Plowman does not fairly disclose treating human subjects, or even mice, post-radiation exposure. Since claims 1, 2 and 4, the claims that had been rejected under Plowman, all refer to post-radiation exposure, these claims are not anticipated by any disclosure of any type of pre-exposure administration, and moreover, the dosage and route of administration in Plowman are not appropriate to support an anticipation rejection.

The undersigned attorney then worked through calculations to show that the 400 mg/kg dosage of Plowman would be toxic in humans. Moreover, the *i.p.* route in mice is not readily translatable to human administration, even though *i.p.* administration is a type of parenteral administration as broadly claimed in claim 4. Also, since proposed amended claim 2 relates to dimesna and not mesna, Plowman cannot anticipate claim 2, a position with which the Examiner

seemed to agree. The Examiner pointed out the broad disclosure in the application of a dosage range of 0.1 mg/kg to 1,000 mg/kg, which includes 400 mg/kg, but the other aspects as claimed distinguish Applicant's method from Plowman.

Moreover, the undersigned attorney pointed out that claim 1 had always required administration of an "effective amount" of the treating drug, and that one skilled in the art would never administer to a patient or human subject an amount of any drug that would be fatal or would have serious adverse side effects. We then reviewed the dosage suggested in the *Drug Facts and Comparisons* reference of record. The undersigned attorney explained how the 400 mg/kg dosage, even though it would be within the broad dosage range disclosed in the application and initially claimed in claim 2, would not be used for mesna. The Examiner's attention was directed to the paragraph bridging pages 4 and 5 of the application where it is stated that dimesna may be used in much greater dosages than mesna, and in view of that, Applicant desires to retain the broad dosage range.

The Examiner mentioned that in her opinion, the Plowman article teaches that mesna should be administered for its radioprotective effect before the patient is exposed to radiation, as claimed in previously pending claims 5 through 16. The undersigned attorney pointed out that Plowman does not render unpatentable the subject matter of at least claims 9 and 12, relating to oral administration, consistent with the Examiner's action in not applying Plowman against claim 3, another claim relating to oral administration. Plowman also does not anticipate claim 16, relating to dimesna, since the reference makes no mention or even a suggestion of dimesna. With respect to the remaining claims 5-10, 11 and 13-15, but focusing on previously pending independent claim 5, the undersigned attorney reiterated the points about the dosage and i.p. route of administration, and further noted the warning aspect of Plowman, which specifically teaches away from using mesna within 12 hours before TBI.

As noted above, claim 5 has been amended herein to recite that the route of administration is intravenous or oral, routes which are not disclosed or suggested in Plowman. Thus, in view of the routes of administration and the effective amount of the compound of formula I to be administered prophylactically to a subject about to be exposed to ionizing radiation, claim 5 and all claims depending therefrom should be patentable over Plowman, which teaches avoiding use of mesna within 12 hours of TBI, thereby teaching away from the present invention.

New claims 17 and 18 specifically exclude mesna from the claimed method, and thus, are not anticipated by Plowman. As a result, claim 17 and claim 18, which depends from claim 17, are not anticipated or otherwise rendered unpatentable over Plowman.

Claim 19 specifically relates to the use of mesna or a pharmaceutically acceptable salt thereof for treatment, being administered “intravenously or orally to the subject.” As discussed above, Plowman simply does not disclose or suggest this administration route, nor does it disclose or suggest “an amount of mesna or a pharmaceutically acceptable salt thereof effective to protect the subject from adverse effects of the ionizing radiation but not so great an amount of mesna or a pharmaceutically acceptable salt thereof as to cause serious adverse effects to the subject,” as set forth in claim 19.

The interview also included a discussion of the sufficiency of the disclosure of the application with respect to the issues of best mode and adequate disclosure of how to use the compound beginning at page 3 of the Detailed Action.

With reference to the best mode rejection, the undersigned attorney pointed out that, in fact, the application discloses the best mode of carrying out the invention as known by the inventor at the time the application was filed. The Examiner’s attention was directed to the specific areas at pages 11-13 of the application where the route of administration, dosage amount and dosage regimen were disclosed for each of pre-exposure administration and post-exposure administration. The Examiner seemed to be satisfied that the best mode has been disclosed.

There was considerable discussion of the “how to use” enablement issue, which the Examiner appeared to agree, in essence, is more in the nature of an assertion of a lack of credible utility issue, since the application contains no specific data showing that any formula I compound has successfully and actually been administered pre- or post-ionizing radiation exposure to prove its effectiveness. The undersigned attorney again used the explanation relating to the best mode, namely, that the application, in fact, discloses credible routes of administration, dosage amounts and dosage regimens for the intended purpose, even if working examples showing actual administration are not presented in the application. However, the Examiner indicated that without additional information, she would be unconvinced that there was a sufficient showing in the application that the compounds would be effective for their intended purpose.

The Examiner said that information from published articles relating to the effectiveness of such compounds, *in vitro* studies that one skilled in the art would accept as adequate

predictors of *in vivo* use, or, preferably, *in vivo* data showing the effectiveness of some of the formula I compounds in recognized laboratory animals would be accepted as substantiating the usefulness of the invention as disclosed and claimed. The Examiner suggested submitting such data with an appropriate declaration with respect to this application.

The Examiner's reliance on the *Lancet* references as enabling references was noted and the Examiner acknowledged that she could not have it both ways with respect to the *Lancet* references, *i.e.*, because the Examiner is relying on the *Lancet* references to show that mesna is effective as a radioprotective agent, then she effectively concedes that such use was known to those skilled in the art, at least for mesna as disclosed in the *Lancet* references, and the rejection based 35 U.S.C. § 112, first paragraph, must fall.

Submitted with this Amendment is a Declaration Under 37 C.F.R. § 1.132 of Steven T. Sonis, D.M.D., D.M.Sc., (the "Sonis Declaration") and the Exhibits attached to the Sonis Declaration, relating to the initial *in vivo* study relating to a compound of formula 1, namely, dimesna, to determine its utility for treating the effects of ionizing radiation. Dr. Sonis was the principal investigator of the study which specifically sought to determine the utility of dimesna in the reduction of oral mucositis induced by a single dose of radiation in a hamster model of oral mucositis developed previously by Dr. Sonis.

As noted in paragraph 4 of the Sonis Declaration, oral mucositis, as represented in his hamster model, occurs in virtually all patients who receive radiation therapy for tumors of the head and neck at certain indicated dosages. As such, the model is appropriate to determine the effectiveness of dimesna in treating a condition created by ionizing radiation. The details of the test procedure and the study results are set forth in the Sonis Declaration and will not be repeated in such detail in this Amendment.

Although there were certain limitations based on the experimental protocol that required statistical significance of effectiveness for two days (Sonis Declaration, paragraphs 9 and 10), the study showed the utility of dimesna as claimed in the present application. Thus, Dr. Sonis concluded in paragraph 11 that based upon the test results and analysis it is his opinion that the mucositis data suggest that there may be some efficacy of dimesna at a 3500 mg/kg dosage in mitigating the radiation effects resulting in oral mucositis. However, he also noted that dimesna appeared to negatively impact weight gain in the hamsters, suggesting that 3500 mg/kg of dimesna may be having some toxic effect, which was not otherwise evaluated.

The evidence provided by the Sonis Declaration further supports the conclusion that the present application adequately discloses a useful method for treating a subject pre- or post-exposure to ionizing radiation.

Since all of the objections and rejections have been overcome, reconsideration and withdrawal of all objections and rejections and an early Notice of Allowance are respectfully solicited.

The Examiner is also respectfully requested to consider and acknowledge such consideration of the references cited in the accompanying Information Disclosure Statement, none of which is believed to adversely affect the patentability of the present invention.

The Examiner is invited to contact the undersigned attorney by telephone if a discussion would advance the prosecution of this application.

Respectfully submitted,

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